REMARKS

1. Based on the Office Communication, the applicants have further amended the claim 1 to clarify the difference between this application and Rieser's prior art by moving the culturing procedure after seeding.

2. As the Office Action indicated, Rieser et al. teach a method "which results in the introduction of mesenchymal stem cells above a bone substitute plate (7) (upper plate) and a bottom plate, which is the bottom of the culture dish." However, the bone substitute plate (7) is not used as a filter. "The bone substitute plate (7) thus has substantially two functions: during the growth of the cartilage, it serves as permeable wall for the cell space (1) and in the finished implant, it serves as anchoring substrate for the cartilage layer," (column 7 lines 18~22). Accordingly, the cells and the bone substitute plate (7) are implanted together. In other words, cells are not recovered from the bone substitute plate (7). Furthermore, as Rieser et al. mentioned, "it is not necessary to isolate specific cell types from donor tissue, i.e. mixture of different cells as usually contained in such tissue can be brought into the cell space as such." (6242247B1 column 5, lines 25-28). The bone substitute plate (7) has a porosity of 300 to 700 μm and a roughness of at least 20 μm (column 12, lines 44-53). Because the size of porosity is too big to serve as a filter and the size of roughness may help cells, including fat cells and red blood cells to adhere, Rieser et al teach a method using a bone substitute plate (7) that does not and should not function as a filter. Moreover, Rieser et al. also indicate that "according to the method described in US Pat. No 5326357 chondrocytes are applied to a layer of filter material (MILLICELL®CM having a pore size of 0.4 μm)...For implants, this kind of inhomogeneous tissue is not suitable." (column 2, lines 43~60).

Since the bone substitute plate (7) of Rieser et al. does not and should not function as a filter, one of ordinary skill in the art at the time of this application was made would have difficulty, if not impossible, to modify the method of isolating mesenchymal stem cells of Caplan et al. to include the introduction of bone marrow aspirate into the cell space and culture dish taught by Rieser et al.

3. The way of culturing taught by Rieser et al. is also different from this application. The cell space of Rieser et al. has at least partly permeable walls and is introduced into a space filled with culture medium for the length of culture period. (column 4 lines 29-31). This application directly cultures the MSC on the upper plate. In other words, the way of culturing is quite different between this application and that of Rieser et al.

4. Directly combining those two prior arts by Caplan et al. and Rieser et al., the method would comprise the steps of

   (i) providing the bone marrow aspirate, which is a cell mixture comprising mesenchymal stem cells (MSC) and other types of cells, (Caplan et al.)

   (ii) seeding the cell mixture comprising a Leukosorb™ filter, which contains pores through which other cells, such as fat cells and red blood cells, pass through, which retains the mesenchymal stem cells, which adhere to the Leukosorb™ filter, (Caplan et al.)

   (iii) eluting the MSC out of the Leukosorb™ filter, (Caplan et al.)

   (iv) introducing the MSC into the cell space, (Rieser et al.)

   (v) culturing the MSC in the cell space, (Rieser et al.)

(vi) implanting MSC together with the bone substitute plate (7) which provides a substrate for the adherence of cells. (Caplan et al.: column 46, lines 30-34 and Rieser et al.: column 7, lines 18-22)

Such combination would be trivial since the fat cells and red blood cells have been filtered out by Leukosorb™ filter. There is no need to introduce the cell space as Rieser et al. taught.

The way of such combination is quite different from this application, which uses the upper plate to filter down such as the fat cells and red blood cells. Furthermore, there is also no such eluting step in this application.

5. Further modification of those two prior arts by Caplan et al. and Rieser et al. to meet this application would comprise the steps of

(i) providing the bone marrow aspirate, which is a cell mixture comprising MSC and other types of cells, (Caplan et al.)

(ii) seeding the cell mixture into a cell space, (Rieser et al.)

(iii) culturing the cell space, (Rieser et al.)

(iv) detaching MSC from the bone substitute plate and recovering MSCs from the cell space. (step not provided by Caplan et al. and Rieser et al.)

As pointed out by Rieser et al., "in order for the bone substitute plate (7) to be able to fulfill the second function... , as shown in FIG. 2, arranged to be stationary with the bone substitute plate (7) facing downward such that the cells settle on the bone substitute plate (7) due to the effect of gravity." (column 7, line 24~34). Since the bone substitute plate (7) is not used as a filter, the red blood cells and fat cells have not been separated during culturing. The efficiency of such modification would be far from that of this application. Therefore, the

result of such modification would be different from this application. There shall be a great difference between such modification and this application.

6. As discussed above, the bone substitute plate (7) taught by Rieser et al. does not function as a filter and would have difficulty to be used a filter due to its pore size and roughness surface. Actually, Rieser et al suggested that "it is not necessary to isolate specific cell types from donor tissue." Furthermore, Rieser et al discredited the filter material in US Pat. No 5326357. Therefore, one of ordinary skill in the art at the time of this application was made would be very possible not to use the bone substitute plate (7) as a filter. Even thought the cell space taught by Rieser et al. functions as a filter, the result of culturing efficiency with together of red blood cells and fat cells is still far behind from this application.

Furthermore, the hydroxyapatite column used by Caplan et al. and the bone substitute plate used by Rieser et al. are both functioned as an anchoring substrate, which is implanted together with MSC. The step of recovering MSC from the upper plate in this application was not taught in these two prior arts. Moreover, the roughness of the bone substitute plate taught by Rieser et al. would also increase the difficulty to recover MSC from it. Therefore, the difference between this application and the prior arts cited would not be obvious.

Accordingly, this application now should be placed in condition of allowance. An early Notice to this effect is respectfully expected.

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